REMARKS

The Invention

The present invention is directed to compositions capable of inducing an immune response to cytotoxic T cell epitopes of a full length viral protein in a mammal. The composition comprises an amount of *Bacillus anthracis* anthrax PA ("PA") and a full length viral protein bound to an APABP ("APABP") sufficient to elicit an MHC class I-mediated cytotoxic T lymphocyte cell ("CTL") immune response specific for the viral protein. The APABP comprises at least the first 250 amino acid residues of the lethal factor of *Bacillus anthracis* and less than all of the amino acid residues of the lethal factor. In some embodiments, the molar ratio of PA to the full length viral protein bound to the APABP is greater than one.

Status of the Claims

After entry of this amendment, claims 1-6 and 30-31 are pending in the application. Claim 1 has been amended. Support for this amendment is found in the specification at, *e.g.*, page 5, lines 9-17.

Claims 1-6, 29, and 31 are rejected under 35 U.S.C. § 103(a) over two combinations of references. These rejections are addressed in detail below in the order presented by the Examiner.

Rejections under 35 U.S.C. § 103

1. Rejection of claims 1-6, 29 and 31 as allegedly obvious over WO 94/18332 ("Leppla *et al.*") in view of WO 95/03414 ("Noteborn *et al.*")

In maintaining this rejection, the Examiner acknowledges that Leppla *et al.* do not teach a full length viral protein bound to APABP, but alleges that in view of the teachings of Noteborn *et al.* it would have been obvious generate such a fusion protein. The rejection further alleges that Leppla *et al.* discloses the functional dosage recited in the claims. Applicants respectfully traverse each of the aspects of this rejection.

Applicants addressed each of the Examiner's concerns in a Declaration under 37 C.F.R. 1.132 by Dr. Stephen Leppla, a well-known authority in the area of bacterial toxins. The Examiner has again rejected the claims, indicating that the arguments presented are not persuasive. In maintaining the rejection of the claims, the Examiner has provided no reasoning as to why his own opinion should be substituted for that of an expert and, thus, has not properly considered the rebuttal evidence presented in the expert declaration.

Accordingly, Applicants urge that Examiner to withdraw the rejection under 35 U.S.C. § 103(a).

2. Rejection of claims 1-6, 30, and 31 as allegedly obvious over Milne *et al.*, Mol. Microbiol. 15:661 (1995) ("Milne *et al.*"), in view of Arora *et al.*, . *Biol. Chem.* 268(5):3334 (1993) ("Arora *et al.*"), Leppla *et al.*, EP 0 532 090, and Donnelly *et al.*, *PNAS USA* 90:3530-3534 (1993) ("Donnelly *et al.*).

In making this rejection, the Examiner asserts that Milne *et al.*, Leppla *et al.*, and Arora *et al.* each disclose that a composition comprising anthrax protective antigen and an antigen bound to APABP (*i.e.* lethal factor or LF) can be used to deliver a target molecule (*i.e.*, the antigen) to the cytoplasm of a cell; that Arora *et al.* teaches that such fusion proteins can be used to present peptides to the MHC class I antigen recognition system; that EP 0 532 090 discloses a fusion protein comprising a cellular recognition domain and a bacterial toxin that has a translocation domain bound to an antigen and that such a fusion protein is capable of eliciting a CTL response; that Donnelly *et al.* discloses a fusion protein comprising a truncated bacterial toxin and an antigenic peptide and that internalization of the peptide induces CTL responses to the peptide. The Examiner further alleges that Arora discloses that large proteins bound to LF do not affect the ability of LF to translocate into the cytoplasm and that Donnelly *et al.* teach that toxin-antigen fusion proteins can comprise whole proteins. The Examiner concludes that, in view of the disclosures of the cited references, one of skill in the art would have been motivated to use whole proteins in a fusion protein comprising an antigen bound to ABABP, that and concludes that the presently claimed invention is obvious in view of the combination of references.

Applicants hereby submit a declaration under 37 C.F.R. 1.132 by Dr. Jay Berzvsky to rebut this rejection (copy enclosed with copy of his Curriculum Vitae as Appendix A). Dr. Berovsky's declaration was previously submitted during the prosecution of U.S.S.N. 08/937,276 (now U.S. Patent No. 6,592,872) the parent of the instant application specifically to clarify for the present Examiner that the combination of Milne *et al.,* Arora *et al.*, (U.S. Patent No. 5,591,631 which is the priority document for Leppla *et al.*), EP 0532 090, and Donnelly *et al.* did not disclose or suggest the use of a binary toxin fusion proteins for delivery of ***full length*** protein antigens to the cytosolic MHC class I antigen processing pathway. As set forth in Dr. Berzovsky's declaration, Milne *et al.*, Arora *et al.*, and Leppla *et al.*, teach the use of anthrax toxins comprising protective antigen and an LF fusion protein in methods for cellular delivery of small peptides, but not full length proteins (*see*, Declaration ¶7). The disclosures of Milne *et al.*, Arora *et al.*, and Leppla *et al.* do not provide any indication or direction as to what parameters are critical for making and using anthrax toxins for delivery of full length proteins to the cytosol for processing and presentation by MHC class I molecules to CTL's (*see*, Declaration ¶7).

Dr. Berzovsky further clarifies that EP 0532 090, and Donnelly *et al.* do not supply the teachings absent from the combination of Milne *et al.*, Arora *et al.*, and Leppla *et al.* EP 0532 090, and Donnelly *et al.* teach methods of inducing an immune response using *Pseudomonas* exotoxin (PE) fused to a 12 amino acid peptide (*i.e.*, from Influenza A matrix protein or nucleoprotein) (*see*, Declaration ¶8). In contrast to the binary anthrax toxin, PE is a single subunit bacterial toxin. Accordingly, EP 0532 090, and Donnelly *et al.* do not teach either the use of binary toxins or full length proteins to induce an immune response. At most the references describe attempts to use PE toxin fusion proteins to translocate peptides into a cell for presentation by the MHC class I pathway (*see*, Declaration ¶8). Moreover, the same authors separately demonstrated that the same PE toxin fusion proteins were likely processed via an alternative, endosomal processing pathway and not the MHC class I cytosolic pathway (*see*, Declaration ¶8, citing Ulmer *et al.*, *Eur. J. Immunol.* 24:1590 (1994), copy enclosed as Appendix B). Thus, if anything, EP 0532 090, and Donnelly *et al.* teach away from the claimed invention.

As further explained by Dr. Berzovsky, the present inventors are the first to show that ***full length*** protein fused to LF and translocated into a cell by anthrax toxin is processed by the cytosolic MHC class I pathway and presented by MHC class I molecules to CTL's (*see*, Declaration, ¶¶ 9 and 10). In addition, the fusion proteins of the invention are more potent in sensitizing cells than peptide epitopes and thus, provide superior results over fusion proteins taught in the art (*see*, Declaration ¶¶ 9 and 10, citing Goletz *et al.*, *PNAS USA* 94:12059 (1997), copy enclosed as Appendix C).

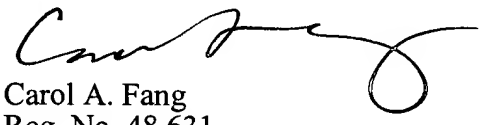
Following submission of Dr. Berzovsky's declaration, the present Examiner withdrew the rejection of the claims under 35 U.S.C. § 103 over Milne *et al.*, Arora *et al.*, Leppla *et al.*, in view of EP 0 532 090, and Donnelly *et al.* (*see*, Office Action mailed March 8, 2002, copy enclosed as Exhibit D). The Examiner has previously acknowledged, in view of the expert's opinion, that the same combination of references does not render a binary toxin fusion protein for delivery of a full length protein antigen obvious. Accordingly, Applicants urge the Examiner to withdraw the rejection of the claims as allegedly obvious under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 925-472-5000.

Respectfully submitted,



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